Vitamin D Supplementation Improves Health-Related Quality of Life and Physical Performance in Children with Sickle Cell Disease and in Healthy Children

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Introduction: No study determined if vitamin D supplementation improves health-related quality of life (HRQL) using pediatric Patient-Reported Outcomes Measurement Information System or physical functioning in type SS sickle cell disease (HbSS).
Method: Subjects with HbSS ($n = 21$) and healthy subjects ($n = 23$) were randomized to daily oral doses (4,000 vs. 7,000 IU) of cholecalciferol (vitamin D_3) and evaluated at 6 and 12 weeks for changes in serum 25 hydroxyvitamin D (25(OH)D), HRQL, and physical functioning.
Results: In subjects with HbSS, significant reductions in pain, fatigue, and depressive symptoms and improved upper-extremity function were observed. In healthy subjects, significant reductions in fatigue and improved upper-extremity function were observed. Significant improvements in peak power and dorsiflexion isometric maximal voluntary contraction torques were observed in both groups. In subjects with HbSS, improved plantar flexion isometric maximal voluntary contraction torques were observed. Both groups saw significant improvement in their total Bruininks-Oseretsky Test of Motor Proficiency score.
Discussion: Daily high-dose vitamin D supplementation for African American children with and without HbSS improved HRQL and physical performance. J Pediatr Health Care. (2020) *XX*, 1−11

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INTRODUCTION

Sickle cell disease (SCD) has a detrimental impact on health-related quality of life (HRQL; Dale, Cochran, Roy, Jernigan, & Buchanan, 2011; Panepinto & Bonner, 2012; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005; Wrotniak, Schall, Brault, Balmer, & Stallings, 2014). Furthermore, compared with healthy similarly aged children, deficits in muscle strength, function, and physical performance in SCD have been reported (Dougherty, Bertolaso, Schall, Smith-Whitley, & Stallings, 2018; Dougherty, Schall, Rovner, Stallings, & Zemel, 2011). Suboptimal vitamin D status is prevalent in children with SCD and associated with poorer growth and disease outcomes (Adegoke, Oyelami, Adekile, & Figueiredo, 2017; Dougherty, Bertolaso, Schall, Smith-Whitley, & Stallings, 2015; Grégoire-Pelchat et al., 2018; Han et al., 2018; McCaskill, Ogunsakin, Hottor, Harville, & Kruse-Jarres, 2018; Osunkwo et al., 2011). However, there have been few studies of the efficacy and safety of vitamin D supplementation in SCD that have been of sufficient size or quality to inform clinical practice (Soe et al., 2017).

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a standardized patient-reported outcome measure in pediatric and adult health with proven reliability and validity developed and supported by the National Institutes of Health (Irwin, Stucky, Langer, et al., 2010; Irwin, Stucky, Thissen, et al., 2010; Lai et al., 2013; Varni et al., 2010; Varni et al., 2014). The pediatric PROMIS self-report scales measure unidimensional health attributes (domains) of depressive symptoms, anxiety, anger, pain interference, peer relationships, fatigue, physical functioning including mobility and upper-extremity function, and asthma impact (Varni et al., 2014). The pediatric PROMIS scales have been validated in children and adolescents with a variety of illnesses, including cancer, kidney disease, asthma, obesity, arthritis, and SCD (Dampier, Barry, et al., 2016; DeWalt et al., 2015). PROMIS pediatric measures are responsive to changes in health status associated with acute vaso-occlusive pain events requiring hospitalization in children with SCD, particularly patient-reported pain, fatigue, depressive symptoms, and physical functioning (Dampier, Jaeger, et al., 2016). No study has determined if vitamin D supplementation can improve HRQL in children with type SS sickle cell disease (HbSS) using PROMIS.

The Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) examines a wide range of neuromuscular motor skills including fine motor precision, balance, coordination, and strength (Bruininks & Bruininks, 2005; Deitz, Kartin, & Kopp, 2007), and has been found to improve in children and young adults with HIV with 12-month high-dose (7,000 IU/day) vitamin D_3 supplementation compared with placebo (Brown et al., 2015). Whether similar improvements in BOTMP scores occur in children with SCD or in healthy children after a shorter term (3 months) of high-dose vitamin D supplementation has not yet been reported.

The purpose of this study was to assess the impact of high-dose vitamin D supplementation over 12 weeks in African American children aged 5−20 years with and without HbSS on (1) HRQL using PROMIS, (2) physical performance including neuromuscular skills using BOTMP, and (3) measures of muscle strength and function.

METHODS

This study was a secondary analysis of a randomized trial, and the main methods and outcomes have previously been reported (Dougherty et al., 2015).

Participants

African American children aged 5−20 years with ($n = 21$) and without ($n = 23$) HbSS were recruited for a vitamin D supplementation study. Children with HbSS were recruited from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (CHOP) and healthy subjects from the CHOP network of primary care centers and the greater Philadelphia region. Exclusion criteria for both groups included: participation in another study impacting serum 25 hydroxyvitamin D (25(OH)D); pregnant or lactating females; other chronic conditions or use of medications affecting growth, dietary intake, or nutritional status; use of vitamin D to treat vitamin D deficiency; and baseline elevated serum calcium concentration. Subjects taking supplements containing vitamin D were not eligible. Those willing to discontinue supplementation with the approval of their medical provider were eligible after a 2-month washout period. Additional exclusion criteria for subjects with HbSS were chronic transfusion therapy, and healthy subjects were body mass index (BMI) > 85th percentile for age and sex (Kuczmarski et al., 2000). Adipose tissue has long been identified as the major site of vitamin D storage (Blum et al., 2008); therefore, children with a weight status category of overweight and/or obese were excluded.

This protocol was approved by the Institutional Review Board at CHOP. Written informed consent was obtained from subjects aged 18−20 years and parents and/or legal guardians of subjects aged < 18 years. Verbal assent was obtained from subjects aged from 6 to < 18 years.

Study Design

Subjects within each group (HbSS or healthy) were randomized in the Spring (April−May), Summer (June−August) or Fall and/or Winter (September−January) to oral daily doses (4,000 vs. 7,000 IU) of cholecalciferol (vitamin D_3) using a double-blind design and evaluated at baseline, 6 and 12 weeks. Safety was monitored weekly by the study team and quarterly by an independent monitoring committee.

Anthropometry, Pubertal Status, and Questionnaires

Anthropometric measurements were obtained in triplicate per standardized techniques (Lohman, Roche, & Martorell,

1988) and the mean used for analysis. BMI was calculated (kilograms/meters^2) from weight using a digital scale (Scale-tronix, White Plains, NY) and standing height using a stadiometer (Holtain, Crymych, United Kingdom). Weight, height, and BMI were compared with reference standards to generate age- and sex-specific *Z*-scores (Kuczmarski et al., 2000). Total body fat and lean body mass were measured using whole-body dual-energy x-ray absorptiometry (DXA; Delphi-A; Hologic, Inc., Bedford, MA) and compared with the Reference Project on Skeletal Development in Children data to generate race- and sex-specific DXA *Z*-scores for lean body mass and fat mass relative to height (Foster, Platt, & Zemel, 2012). At baseline, pubertal status, according to the criteria of Tanner (Tanner, 1962), was determined using a validated self-assessment questionnaire (Morris & Udry, 1980). Adherence (Dougherty et al., 2015) was assessed by questionnaire at 6 and 12 weeks and phone calls at weeks 1, 3, 5, 8, and 10. Subjects were interviewed at each visit, documenting the intensity and frequency of any adverse events (Dougherty et al., 2015).

Biochemistry and Hematology

Serum 25(OH)D was determined using liquid chromatography-tandem mass spectrometry (Clinical Laboratory, CHOP) with intra and interassay coefficients of variation below 7%. The justification for defining vitamin D status (25(OH)D concentration) has been previously reported (Dougherty et al., 2015): sufficient, ≥ 32 ng/mL; insufficient, < 32−20 ng/mL; and deficient, < 20 ng/mL. Hematologic status was assessed by complete blood count for all subjects, and fetal hemoglobin was assessed in HbSS only according to standardized techniques. Serum high-sensitivity C-reactive protein (HS-CRP) was assessed in all subjects as an indicator of inflammatory status. Subjects with HbSS were categorized as receiving or not receiving hydroxyurea therapy during the study.

Health-Related Quality of Life

HRQL was assessed using the following PROMIS pediatric short forms: depressive symptoms, fatigue, pain, mobility, peer relationships, and upper-extremity function. For PROMIS assessment of item response theory-based *t* scores (population mean, 50; SD, 10) in the depressive symptoms, fatigue, and pain domains, a higher *t*-score indicates a worse outcome and, in the mobility, peer relationships, and upper-extremity function domains lower *t* scores indicate a worse outcome.

Neuromuscular Motor Skills

The BOTMP (Bruininks & Bruininks, 2005) consists of 14 measures that represent eight neuromuscular motor skill domains. These include fine motor precision (line drawing, fold paper), fine motor integration (copy square, copy star), manual dexterity (penny transfer), bilateral coordination (jump in place, tap feet and fingers), balance (line walk, one leg balance), speed and agility (one leg hop), upper limb coordination (drop and/or catch ball, dribble ball), and strength (push-ups, sit-ups). Measurement details and scoring for each motor skill are described elsewhere (Bruininks & Bruininks, 2005). The total BOTMP score combines results from all skills for an overall score of motor proficiency, and higher scores indicate greater neuromuscular motor skill proficiency. Test-retest reliability ($r = .8$) and criterion-related validity, when compared with other measures of motor performance ($r = .74$), are excellent for the BOTMP (Deitz et al., 2007).

Muscle Strength and Function

All subjects completed a 5-minute warm-up period of treadmill walking at a comfortable self-selected speed at 0% grade. Next, maximal handgrip strength of the right and left hand was measured in kilograms with a handgrip dynamometer (Takei Scientific Instruments, Co., Ltd., Tokyo, Japan). Hand dominance was determined by asking which hand was used to hold a pencil. The participants stood upright with the shoulder adducted, holding the dynamometer, not touching the trunk. The handle was adjusted to the hand size of the child, and no extraneous body movement was allowed during testing. For each hand, three maximal effort trials lasting 4−5 s interspersed with 60 s rests were performed (verbal encouragement provided).

Peak power in watts was calculated from the force-time curve and velocity of the center of mass during a maximal vertical squat jump using a Kistler Quattro Jump Portable Force Plate System (Model 9290AD; Kistler Instrument Corporation, Amherst, NY). Participants completed three warm-ups followed by three maximal vertical jumps from an initial static squat position with knees at 90° flexion and arms akimbo. The highest value was used for analysis (McKay et al., 2005; Toumi et al., 2007).

Muscle torque was assessed using the Biodex Multi-Joint System 3 Pro (Biodex Medical Systems, Inc., Shirley, NY). High intrarater (0.97−0.99) and interrater (0.93−0.96) intraclass correlation coefficients have been reported for this method testing various body joints (Leggin, Neuman, Iannotti, Williams, & Thompson, 1996). Before testing, each subject was familiarized with the test procedures. Plantar and dorsiflexion isometric maximal voluntary contraction (MVC) torques of the left ankle were measured in triplicate at each of four angles (−10°, 0°, 10°, and 20°) and the highest value in Newton meters (Nm) recorded for dorsiflexion and plantarflexion at each angle. Isokinetic knee flexion and extension peak torque (Nm) was measured in triplicate at 1.05 rad/s (60°/s) and the highest value recorded for extension and flexion of the left knee.

Statistical Analyses

All variables were tested for normality, and nonparametric tests were used as appropriate. At baseline, differences between groups (HbSS vs. healthy), at different doses (HbSS vs. healthy at 4,000 IU; HbSS vs. healthy at 7,000 IU) and within-group at different doses (4,000 vs. 7,000 IU in HbSS; 4,000 vs. 7,000 IU in healthy) were determined by using a Student's *t* test or Wilcoxon rank-sum test for continuous

TABLE 1. Subject characteristics at baseline and vitamin D concentrations and baseline and 12 weeks

Characteristics	HbSS[a]all	HbSS 4,000 IU/day	HbSS 7,000 IU/day	Healthy all	Healthy 4,000 IU/day	Healthy 7,000 IU/day
n	21	12	9	23	11	12
Age, years	11 ± 4[b]	11 ± 4	10 ± 5	10 ± 4	9.7 ± 4.3	10.9 ± 3.5
Sex, % female	57	58	56	43	27	58
Tanner, % 1 or 2	67	67	67	57	64	50
On hydroxyurea, %	43	33	56	—	—	—
Height, cm	137.6 ± 20.5	139.2 ± 21.6	135.4 ± 20.0	141.5 ± 20.5	137.5 ± 23.5	145.1 ± 17.5
Height *Z*-score	−0.5 ± 1.2	−0.7 ± 1.3	−0.2 ± 0.9	0.4 ± 1.0[a]	0.3 ± 0.9	0.5 ± 1.0
Weight, kg	33.7 ± 15.4	32.6 ± 13.6	35.2 ± 18.3	43.9 ± 20.8	44.1 ± 27.4	43.7 ± 13.5
Weight *Z*-score	−0.7 ± 1.2	−1.1 ± 1.1	−0.0 ± 1.1[b]	0.8 ± 1.1[a]	0.9 ± 1.0	0.7 ± 1.3
BMI	16.9 ± 3.6	16.0 ± 2.2	18.0 ± 4.8	20.7 ± 5.7[a]	21.0 ± 6.8	20.4 ± 4.7
BMI *Z*-score	−0.6 ± 1.1	−1.0 ± 0.9	−0.0 ± 1.1[b]	0.7 ± 1.1[a]	0.8 ± 1.1	0.6 ± 1.2
LBM—DXA, kg	25.0 ± 9.8	24.5 ± 9.5	25.5 ± 10.8	31.1 ± 13.9	30.9 ± 18.2	31.1 ± 9.2
FM—DXA, kg	8.8 ± 6.1	8.0 ± 4.2	9.8 ± 8.2	13.0 ± 8.8	13.3 ± 10.9	12.8 ± 6.9
LBM-for-height *Z*-score	−1.9 ± 1.0	−2.4 ± 0.8	−1.3 ± 1.0[b]	−0.9 ± 1.4[a]	−0.9 ± 1.5	−0.9 ± 1.3
FM-for-height *Z*-score	0.2 ± 0.6	0.0 ± 0.2	0.4 ± 0.6	0.8 ± 0.8[a]	1.0 ± 0.5	0.6 ± 1.0
FM, %	24.6 ± 5.1	24.0 ± 3.0	25.4 ± 7.2	28.0 ± 8.7	27.3 ± 8.6	28.5 ± 9.1
Total 25(OH)D, ng/mL	19.2 ± 7.2	18.0 ± 7.0	20.8 ± 7.5	22.3 ± 9.3	22.8 ± 8.4	21.9 ± 10.4
Total 25(OH)D at 12 weeks, ng/mL	44.9 ± 26.6[c]	38.1 ± 21.0[c]	53.1 ± 31.3[c]	42.2 ± 17.8[c]	43.7 ± 18.4[c]	40.5 ± 18.1[c]
Force plate						
Peak power, watts/kg	30.8 ± 3.7	29.6 ± 4.3	32.6 ± 1.8	33.8 ± 6.8	33.5 ± 5.8	34.2 ± 7.9
Peak power, watts	1,054 ± 478	953 ± 401	1,207 ± 568	1,488 ± 811[a]	1,513 ± 1,098	1,465 ± 467
Jump height	25.3 ± 5.2	23.6 ± 5.7	27.7 ± 3.3	28.0 ± 8.5	27.1 ± 8.2	28.8 ± 9.0
Biodex ankle: plantar flexion isometric MVC torques, Nm						
−10°	44.7 ± 22.2	43.7 ± 19.1	46.0 ± 26.9	53.6 ± 36.9	52.2 ± 46.4	54.8 ± 25.0
Biodex ankle: dorsiflexion isometric MVC torques, Nm						
−10°	9.8 ± 5.7	9.6 ± 5.9	10.2 ± 5.7	12.5 ± 6.9	13.1 ± 8.7	11.9 ± 4.7
0°	12.3 ± 7.3	11.6 ± 7.4	13.1 ± 7.4	15.7 ± 10.7	15.4 ± 12.0	15.9 ± 9.9
10°	13.3 ± 8.3	12.9 ± 7.5	13.9 ± 9.8	16.9 ± 12.1	17.4 ± 15.7	16.5 ± 8.1
20°	14.9 ± 9.3	13.9 ± 7.9	16.2 ± 11.3	18.1 ± 13.3	19.2 ± 18.0	17.1 ± 7.6
Biodex knee: extension peak torque, Nm						
60°/sec	49.6 ± 27.6	48.8 ± 23.3	51.7 ± 34.0	65.8 ± 44.1	64.3 ± 57.9	67.1 ± 29.0
Biodex knee: flexion peak torque, Nm						
60°/sec	22.4 ± 13.3	21.7 ± 9.7	23.3 ± 17.7	25.5 ± 14.7	22.5 ± 16.7	28.2 ± 12.7
Dominate hand max, kg	15.6 ± 8.6	14.8 ± 8.5	16.7 ± 9.0	22.7 ± 9.6[a]	21.4 ± 11.3	23.9 ± 8.0
Right hand max, kg	15.6 ± 8.6	14.8 ± 8.5	16.7 ± 9.0	20.8 ± 10.0	19.3 ± 11.5	22.1 ± 8.8
Left hand max, kg	15.2 ± 7.6	14.8 ± 6.4	15.8 ± 9.4	19.8 ± 10.4	19.6 ± 12.3	20.1 ± 8.9
BOT						
Total score	61.5 ± 14.0	64.3 ± 9.9	57.8 ± 18.1	62.3 ± 15.2	57.9 ± 16.0	66.3 ± 13.9
Transferring pennies	12.3 ± 3.3	13.2 ± 2.1	11.2 ± 4.3	12.4 ± 4.6	10.9 ± 4.9	13.6 ± 4.1
One-legged stationary hop	36.3 ± 7.9	36.8 ± 8.2	35.8 ± 8.0	31.3 ± 10.8	33.5 ± 10.2	29.3 ± 11.3
Dropping and catching a ball—both hands	4.2 ± 1.7	4.7 ± 1.2	3.6 ± 2.1	4.4 ± 1.5	4.5 ± 1.5	4.3 ± 1.5

(continued on next page)

TABLE 1. *(Continued)*

Characteristics	HbSS[a]all	HbSS 4,000 IU/day	HbSS 7,000 IU/day	Healthy all	Healthy 4,000 IU/day	Healthy 7,000 IU/day
Dribbling a ball—alternating hands	5.1 ± 4.3	6.0 ± 4.2	3.9 ± 4.2	6.3 ± 3.7	5.1 ± 3.8	7.5 ± 3.4
Push-ups	11.9 ± 8.5	14.1 ± 8.6	9.0 ± 8.0	16.0 ± 8.7	15.2 ± 8.5	16.7 ± 9.1
Sit-ups	11.9 ± 9.6	11.3 ± 8.4	12.8 ± 11.5	13.5 ± 7.1	11.2 ± 6.2	15.7 ± 7.5
Fetal hemoglobin, %	12.4 ± 5.8	9.7 ± 5.1	15.1 ± 5.4[b]	—	—	—
HS-CRP, mg/L	3.0 ± 2.6	1.9 ± 1.9	4.0 ± 2.7	1.1 ± 1.5[a]	0.7 ± 0.7	1.5 ± 1.9
Hemoglobin, g/dL	8.4 ± 1.0	8.1 ± 1.2	8.7 ± 0.8	13.0 ± 1.1[a]	13.1 ± 1.2	13.0 ± 1.1
Hematocrit, %	25.9 ± 3.1	24.9 ± 3.3	27.0 ± 2.6	39.8 ± 3.1[a]	40.5 ± 3.7	39.3 ± 2.6
Platelets, $\times 10^3/\mu L$	522 ± 158	599 ± 174	436 ± 80[b]	303 ± 64[a]	295.1 ± 60.6	310.4 ± 67.8

Note. *HbSS, type SS sickle cell disease; LBM, lean body mass; DXA, dual-energy x-ray absorptiometry; FM, fat mass; 25(OH)D, 25-hydroxyvitamin D; MVC, maximal voluntary contraction; BOT, Bruininks-Oseretsky Test of Motor Proficiency; HS-CRP, high-sensitivity C-reactive protein. Values are mean ± standard deviation.*

[a] *p < .05, HbSS vs. healthy.*

[b] *p < .05, 4,000 vs. 7,000 IU/day in HbSS.*

[c] *p < .05, 12 weeks vs. baseline.*

variables and Fisher exact or χ^2 test for categorical variables. Longitudinal-mixed-effects (LME) analyses (Laird & Ware, 1982) were used to examine change over time and whether patterns of change were different between HbSS versus healthy groups, with vitamin D dose group combined. The preliminary analysis did not find any statistically significant difference by dose in physical performance or HRQL outcomes; thus, dose groups were combined. These analyses were made using the intention-to-treat model in which all subjects are included regardless of adherence to the study protocol. Similar to multiple linear regression analysis, LME analysis allows for multiple observations per subject. LME assumes that observations measured from the same subject are dependent and, therefore, the regression coefficients vary across subjects and are considered random. In addition, it allows for unequal intervals between visits, uses data from all subjects, even when some study visits were missed, and accommodates both fixed and random effects. Parameter estimates, as in regression analysis, indicate the contribution of the independent variable to the model. For these LME analyses which controlled for baseline value, the subject was treated as a random effect and measurement and time as fixed effects. All statistical analyses were performed by using Stata 14 (Stata, Corp., College Station, TX). The results were considered significant at $p < .05$ (unless otherwise indicated), and data are presented as means ± SDs (normal distribution).

RESULTS

Twenty-one African American children with HbSS and 23 healthy African American controls of similar age and sex (Table 1) completed the study, receiving either 4,000 or 7,000 IU/day vitamin D_3 for 12 weeks. Serum 25(OH)D at baseline was similar in HbSS (19.2 ± 7.2 ng/mL) and healthy children (22.3 ± 9.3 ng/mL). Children with HbSS had significantly poorer growth status for height, weight, and BMI than the healthy children at baseline.

High-dose vitamin D supplementation was efficacious in improving vitamin status in both groups. After 12 weeks of supplementation, the mean increase in 25(OH)D was 25.6 ± 22.3 ng/mL in subjects with HbSS and 20.5 ± 17.5 ng/mL in healthy subjects (both $p < .05$) In subjects with HbSS, fetal hemoglobin significantly increased (12.4 ± 5.8 vs. 14.0% ± 6.2 percentage points), and serum high-sensitivity C-reactive protein decreased (3.0 ± 2.6 vs. 2.0 ± 1.7 mg/L) with vitamin D_3. Ten children (48%) were receiving hydroxyurea therapy at the time of the study.

At baseline, based on PROMIS domain *t* scores, healthy children reported significantly less pain, fatigue, and had greater mobility than children with HbSS ($p < .05$). After 12-week vitamin D supplementation (Table 2), children with HbSS showed significant ($p < .05$) declines in pain, fatigue, and depressive symptoms *t* scores and an increased upper-extremity function *t*-score, with no difference in mobility or peer relationships. Healthy subjects also had a significant ($p < .05$) decline in fatigue and improvement in upper-extremity function *t* scores, with no change in pain, depressive symptoms, mobility, or peer relationships *t* scores.

TABLE 2. Patient-Reported Outcomes Measurement Information System (PROMIS)

Outcomes	*n*	Baseline	*n*	6 weeks	*n*	12 weeks
Pediatric physical function—upper-extremity *t*-score						
Healthy	23	50.6 ± 8.8	20	52.5 ± 6.7	19	53.2 ± 6.4[a]
HbSS	21	45.9 ± 10.9	21	47.8 ± 9.5	20	51.2 ± 8.7[b]
Pediatric physical function—mobility *t*-score						
Healthy	23	57.8 ± 3.3	20	58.1 ± 2.9	19	57.5 ± 3.7
HbSS	21	53.1 ± 6.2[c]	21	55.2 ± 5.1[d]	20	55.7 ± 5.4
Pediatric peer relationships *t*-score						
Healthy	23	56.0 ± 7.3	20	57.2 ± 7.8	19	56.1 ± 9.2
HbSS	21	56.9 ± 7.1	21	58.2 ± 8.5	20	57.8 ± 11.0
Pediatric pain impact *t*-score						
Healthy	23	48.6 ± 8.7	20	49.9 ± 10.1	19	48.9 ± 7.3
HbSS	21	54.4 ± 13.3[c]	21	52.7 ± 13.2[d]	20	48.4 ± 14.8[b]
Pediatric fatigue *t*-score						
Healthy	23	40.3 ± 10.3	20	43.3 ± 12.4	19	36.3 ± 10.0[a]
HbSS	21	51.7 ± 11.4[c]	21	48.6 ± 10.2	20	46.4 ± 14.0[b,e]
Pediatric depressive symptoms *t*-score						
Healthy	23	41.5 ± 8.2	20	37.4 ± 7.6[f]	19	39.9 ± 9.4
HbSS	21	43.1 ± 8.1	21	39.1 ± 5.8[g]	20	39.1 ± 7.3[b]

Note. *HbSS, type SS sickle cell disease. Values are mean ± standard deviation.*
[a] *p < .05, HbSS vs. healthy at 12 weeks.*
[b] *p < .05, 6 weeks vs. baseline in Healthy.*
[c] *p < .05, 6 weeks vs. baseline in HbSS.*
[d] *p < .05, 12 weeks vs. baseline in Healthy.*
[e] *p < .05, 12 weeks vs. baseline in HbSS.*
[f] *p < .05, HbSS vs. healthy at baseline.*
[g] *p < .05, HbSS vs. healthy at 6 weeks.*

Children with HbSS showed steady and incremental improvement in *t* scores from baseline to 6 and 12 weeks, whereas the patterns of change varied in healthy children over the domains.

Healthy children did not differ from children with HbSS at baseline, 6 weeks, or 12 weeks in neuromuscular motor skills based on BOTMP (Table 3). After 12 weeks of vitamin D supplementation, children with HbSS improved significantly ($p < .05$) in the total BOTMP score, and particularly for strength (push-ups and sit-ups) and upper limb coordination (drop and/or catch and dribble ball). Healthy children also showed significant ($p < .05$) improvement in the total BOTMP score with supplementation and particularly for manual dexterity (penny transfer), fine motor integration (copy star), and speed and agility (one leg hop).

At baseline, children with HbSS had significantly lower dominant hand maximal handgrip strength, peak power, and plantar flexion isometric MVC torques at 10° and 20° angles (Table 4). After 12-week vitamin D supplementation (Table 4), significant improvements ($p < .05$) in peak power and dorsiflexion isometric MVC torques at the 20° angle were observed in both groups. In addition, in children with HbSS, significant improvements ($p < .05$) in plantar flexion isometric MVC torques at the −10° angle and dorsiflexion isometric MVC torques at the −10° and 0° angles were observed.

DISCUSSION

Daily high-dose vitamin D supplementation for African American children with and without HbSS improved HRQL and physical performance. These improvements were accompanied by improvement in serum vitamin D status for both groups, and, in children with HbSS, improvement in clinical status (fetal hemoglobin) and inflammatory status. These findings highlight the beneficial pleiotropic effects of vitamin D supplementation for children's physical and mental development and also suggest possible disease-specific improvements in SCD with supplementation.

Vitamin D deficiency is prevalent in people with SCD and is linked to acute and chronic pain and bone fracture in this population (Adegoke et al., 2017; Han et al., 2018; Osunkwo et al., 2011). Vitamin D status has also been associated with greater SCD disease severity (Grégoire-Pelchat et al., 2018; McCaskill et al., 2018). High-dose vitamin D_3 supplementation is safe and efficacious in SCD. We have previously demonstrated that 12-week high-dose vitamin D_3 supplementation (4,000 or 7,000 IU/day) was safe and efficacious in improving serum 25(OH)D in both children with HbSS and healthy children (Dougherty et al., 2015). Vitamin D deficiency (25(OH)D of < 20 ng/mL) was eliminated for both groups receiving the highest D_3 dose. For children with HbSS, vitamin supplementation improved their clinical status with increased fetal hemoglobin, decreased inflammatory status, and reduced platelet counts (Dougherty et al., 2015). A 2-year supplementation (monthly oral 100,000 or 12,000 IU) study improved annual rates of respiratory illness in children aged 3−20 years with SCD (reduction of > 50%; Lee et al., 2018). Although other vitamin D supplementation trials in SCD have been conducted, many have not been of sufficient size or quality to inform clinical practice. Future

TABLE 3. Bruininks-Oseretsky Test of motor proficiency (BOT) outcomes

Outcomes	n	Baseline	n	6 weeks	n	12 weeks
Total score						
Healthy	23	62.3 ± 15.2	20	64.8 ± 14.4	19	67.2 ± 10.3[a]
HbSS[a]	21	61.5 ± 14.0	21	64.5 ± 11.5	20	66.4 ± 10.3[b]
Subscales						
Fine motor precision						
Drawing lines through paths—crooked						
Healthy	23	2.6 ± 4.9	20	3.6 ± 6.7	19	1.9 ± 3.7
HbSS	21	0.6 ± 1.0	21	0.9 ± 1.5	20	1.1 ± 2.3
Folding paper						
Healthy	23	8.9 ± 3.5	20	8.8 ± 4.4	19	9.6 ± 3.3
HbSS	21	8.4 ± 4.0	21	8.4 ± 3.8	20	8.7 ± 3.5
Fine motor integration						
Copying a square						
Healthy	23	4.5 ± 1.2	20	4.1 ± 1.6	19	4.9 ± 0.2
HbSS	21	4.6 ± 1.2	21	4.6 ± 1.1	20	4.6 ± 0.8
Copying a star						
Healthy	23	2.5 ± 2.2	20	3.1 ± 2.1	19	3.3 ± 1.8[a]
HbSS	21	2.9 ± 2.0	21	3.5 ± 1.6	20	3.6 ± 1.5
Manual dexterity						
Transferring pennies						
Healthy	23	12.3 ± 4.6	20	13.1 ± 4.4	19	13.2 ± 4.0[a]
HbSS	21	12.3 ± 3.3	21	12.7 ± 4.0	20	13.1 ± 4.6
Bilateral coordination						
Jumping in place—same sides synchronized						
Healthy	23	4.8 ± 1.0	20	5.0 ± 0.0	19	5.0 ± 0.0
HbSS	21	4.8 ± 1.1	21	4.8 ± 0.9	20	4.8 ± 1.1
Tapping feet and fingers—same side synchronized						
Healthy	23	9.4 ± 2.1	20	10.0 ± 0.0	19	10.0 ± 0.0
HbSS	21	10.0 ± 0.0	21	10.0 ± 0.0	20	10.0 ± 0.0
Balance						
Walking forward online						
Healthy	23	6.0 ± 0.2	20	6.0 ± 0.0	19	6.0 ± 0.0
HbSS	21	5.8 ± 1.1	21	6.0 ± 0.0	20	6.0 ± 0.0
Standing on one leg on a balance beam—eyes open						
Healthy	23	7.5 ± 3.1	20	8.0 ± 2.8	19	8.6 ± 2.7
HbSS	21	8.6 ± 2.6	21	8.7 ± 2.1	20	8.8 ± 2.4
Speed and agility						
One-legged stationary hop						
Healthy	23	31.3 ± 10.8	20	32.1 ± 11.5	19	36.2 ± 6.2[a]
HbSS	21	36.3 ± 7.9	21	33.9 ± 7.2	20	37.6 ± 7.6
Upper limb coordination						
Dropping and catching a ball—both hands						
Healthy	23	4.4 ± 1.5	20	4.7 ± 1.2	19	4.7 ± 0.7
HbSS	21	4.2 ± 1.7	21	4.2 ± 1.4	20	4.7 ± 0.7[b]
Dribbling a ball—alternating hands						
Healthy	23	6.3 ± 3.7	20	6.9 ± 3.2	19	7.3 ± 3.2
HbSS	21	5.1 ± 4.3	21	5.5 ± 3.6	20	5.8 ± 3.9[b]
Strength						
Push-ups						
Healthy	23	16.0 ± 8.7	20	18.1 ± 7.2	19	15.2 ± 6.6
HbSS	21	11.9 ± 8.5	21	16.0 ± 5.4	20	16.3 ± 5.4[b]
Sit-ups						
Healthy	23	13.5 ± 7.1	20	18.2 ± 6.8	19	16.9 ± 6.1
HbSS	21	11.9 ± 9.6	21	16.6 ± 6.7	20	17.8 ± 7.9[b]

Note. *HbSS, type SS sickle cell disease. Values are mean ± standard deviation.*
[a] *$p < .05$, 12 weeks vs. baseline in Healthy.*
[b] *$p < .05$, 12 weeks vs. baseline in HbSS.*

large-scale randomized, double-blind, placebo-controlled trials of vitamin D supplementation are needed.

Children with HbSS, as well as those with other chronic illnesses, have poorer patient-reported HRQL than healthy children (Dale et al., 2011; Panepinto et al., 2005; Panepinto & Bonner, 2012; Wrotniak et al., 2014). Results from the present study are in agreement. In adults and children, the severity of SCD has been associated with worse PROMIS

TABLE 4. Muscle strength, power, and torque outcomes

Outcomes	*n*	Baseline	*n*	6 weeks	*n*	12 weeks
Force plate						
Peak power, watts						
Healthy	23	1,487.6 ± 811.1	19	1,662.2 ± 848.6	19	1,658.3 ± 888.9[a]
HbSS	20	1,054.3 ± 477.8[b]	20	1,066.3 ± 577.9c	20	1,071.1 ± 537.2[a,d]
Jump height, cm						
Healthy	23	28.0 ± 8.5	19	27.8 ± 7.6	19	27.7 ± 8.3
HbSS	20	25.2 ± 5.2	20	25.1 ± 5.5	20	25.6 ± 5.8
Biodex ankle						
Plantar flexion isometric MVC torques, Nm						
−10°						
Healthy	21	53.6 ± 36.9	19	62.3 ± 44.2	18	64.6 ± 42.5
HbSS	21	44.7 ± 22.2	21	50.7 ± 33.1	20	52.5 ± 31.6[d]
0°						
Healthy	22	50.0 ± 31.0	20	52.0 ± 31.8	19	53.7 ± 28.9
HbSS	21	39.0 ± 20.0	21	43.3 ± 26.3	20	39.6 ± 21.6
10°						
Healthy	23	42.2 ± 24.7	20	43.4 ± 24.5	19	44.1 ± 23.2
HbSS	21	27.3 ± 17.1[b]	21	34.1 ± 21.4	20	31.1 ± 17.0
20°						
Healthy	23	33.5 ± 19.5	20	32.7 ± 17.4	19	35.5 ± 19.0
HbSS	21	21.2 ± 11.8[b]	21	23.6 ± 16.2	20	23.0 ± 13.5[a]
Dorsiflexion isometric MVC torques, Nm						
−10°						
Healthy	21	12.5 ± 6.9	19	13.6 ± 8.9	18	13.5 ± 9.1
HbSS	21	9.8 ± 5.7	21	9.8 ± 4.8	20	11.6 ± 6.7[d]
0°						
Healthy	22	15.7 ± 10.7	20	16.4 ± 11.1	19	17.0 ± 10.0
HbSS	21	12.3 ± 7.3	21	12.6 ± 7.9	20	14.5 ± 9.0[d]
10°						
Healthy	23	16.9 ± 12.1	20	19.8 ± 13.0	19	22.6 ± 17.5
HbSS	21	13.3 ± 8.3	21	15.4 ± 9.0	20	15.9 ± 9.9
20°						
Healthy	23	18.1 ± 13.4	20	20.5 ± 12.4	19	21.6 ± 12.9[e]
HbSS	21	14.9 ± 9.3	21	15.5 ± 8.6	20	17.3 ± 10.3[d]
Biodex knee						
Extension peak torque, Nm						
60°/sec						
Healthy	23	65.8 ± 44.1	20	69.0 ± 44.2	19	64.3 ± 42.8
HbSS	21	49.6 ± 27.6	21	47.8 ± 27.6	20	41.8 ± 21.1[a]
Flexion peak torque, Nm						
60°/sec						
Healthy	23	25.5 ± 14.7	20	29.2 ± 19.2	19	29.8 ± 20.4
HbSS	21	22.4 ± 13.3	21	23.2 ± 11.7	20	21.7 ± 11.5
Handgrip						
Dominate hand max, kg						
Healthy	23	22.7 ± 9.6	20	21.9 ± 9.9	19	24.1 ± 9.2
HbSS	21	15.6 ± 8.6[b]	21	16.2 ± 7.9[c]	20	16.5 ± 7.8[a]

Note. *HbSS, type SS sickle cell disease; MVC, maximal voluntary contraction. Values are mean ± standard deviation.*
[a] *$p < .05$, HbSS vs. healthy at 12 weeks.*
[b] *$p < .05$, HbSS vs. healthy at baseline.*
[c] *$p < .05$, HbSS vs. healthy at 6 weeks.*
[d] *$p < .05$, 12 weeks vs. baseline in HbSS.*
[e] *$p < .05$, 12 weeks vs. baseline in Healthy.*

t scores in many domains compared with the general population (Dampier, Barry, et al., 2016; Dampier, Jaeger, et al., 2016; Keller, Yang, Treadwell, & Hassell, 2017; Reeve et al., 2018). In the present study, improvements ranging from 4 to 6 *t*-score points in pain, fatigue, depression, and upper-extremity function in HbSS after a relatively short period (12 weeks) of supplementation are considered major changes, given that the minimally important difference in PROMIS *t* scores is considered a change of three points (Reeve et al., 2018; Thissen et al., 2016).

Pain and fatigue are particularly debilitating symptoms for children with HbSS and have a particular impact on patient-reported outcomes and quality of life (Ameringer, Elswick, & Smith, 2014; Anderson, Allen, Thornburg, & Bonner, 2015;

Bakshi, Lukombo, Belfer, & Krishnamurti, 2018; Bakshi, Ross, & Krishnamurti, 2018; Dampier, Jaeger, et al., 2016; Dewalt et al., 2013). In a meta-analysis, vitamin D was shown to decrease pain scores and improve pain in people with widespread chronic pain (Yong, Sanguankeo, & Upala, 2017). The results of this study suggest that high-dose vitamin D holds promise to improve pain and fatigue symptoms and overall HRQL in children with SCD, however further study is needed to show sustained or enhanced improvement with longer term supplementation.

High-dose vitamin D_3 may play a role in improving physical performance in children with and without chronic illness. Vitamin D receptors are present in the nucleus and on the membrane of human muscle cells. Genomic effects are through binding of 1,25-dihydroxyvitamin D to the nuclear vitamin D receptor and include gene transcription of mRNA and protein synthesis influencing muscle calcium transport and phospholipid metabolism. Nongenomic effects act via second messenger pathways to regulate intracellular calcium transport and stimulate muscle cell proliferation and growth (Bartoszewska, Kamboj, & Patel, 2010). In vitamin D deficient adults, the atrophy of type II fast-twitch muscle fibers, which are essential for rapid movement in emergencies and routine activities of daily living, is reversible with vitamin D supplementation (Ceglia, 2009; Hamilton, 2010). Moreover, several randomized controlled trials in older healthy adults demonstrated an improvement in neuromuscular functioning, including balance, reaction time, and muscle strength and performance with vitamin D supplementation (Cannell, Hollis, Sorenson, Taft, & Anderson, 2009). In the present study, significant improvement in neuromuscular motor skills (total BOTMP) with vitamin D supplementation was evident for both children with HbSS and healthy children, although the improvements tended to be in different domains for the two groups. This improvement is consistent with the significant reduction in fatigue all children reported in PROMIS. In addition, for children with HbSS, the patient-reported improvement in upper-extremity function (PROMIS) is consistent with improvement seen in upper limb coordination in the BOTMP.

Children with HbSS have been shown to have muscle strength, power, and torque deficits compared with healthy children of similar age, race, and sex (Dougherty et al., 2011; Dougherty et al., 2018). In this study, we report improvements in muscle power and torque with vitamin D_3 supplementation for both children with HbSS and healthy children. These improvements in tests of muscle strength and function are consistent with reported reductions in both pain and fatigue, and improvements in physical function in children with HbSS and the reported reduction in fatigue and improvement in physical function in healthy children based on PROMIS. Future studies investigating the potential of vitamin D to improve physical functioning and HRQL in SCD are warranted.

In conclusion, daily high-dose vitamin D supplementation improved HRQL, muscle strength, and physical performance in children with and without HbSS. The significance of these findings relates to overall health; vitamin D supplementation may prove to be an effective and feasible treatment for symptoms and prevention of complications for people of all ages living with HbSS in the United States and around the world. In this study cohort, only the 7,000 IU/day dose effectively treated deficiency (25(OH)D of < 20 ng/mL) in both HbSS and healthy participants. This finding highlights the need for full-scale randomized, double-blind placebo-controlled trials to test the impact of higher D_3 doses on HRQL and physical performance in children and young adults with HbSS and their healthy counterparts.

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